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Combined in situ hypothermic liver preservation and cardioplegia for resection of hepatoblastoma with intra-atrial extension in a 3 year old child

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ABSTRACT

Cure of hepatoblastoma requires complete macro- and microscopic resection of the tumor, without tumor rupture. In case of hepatoblastoma with intra-atrial tumor extension (ITE), "en bloc" resection of the hepatic tumor and ITE, with minimal risk of postoperative liver failure, constitutes a surgical challenge. We report on a 3 year old child with hepatoblastoma of the right liver lobe, and ITE through the upper Inferior Vena Cava. Initial chemotherapy (SIOPEL IV HR) induced good response, but tumor persisted inside the right atrium with tight adhesions to the cardiac wall. "En bloc" right extended hepatectomy and removal of the ITE with reconstruction of the atrial and caval wall with autologous pericardial patch was performed under normothermic extracorporeal circulation and cardioplegia, combined with in situ hypothermic liver preservation of the remaining left liver. Complete tumor resection was achieved without tumor rupture. Postoperative liver function was immediately good and adjuvant chemotherapy was resumed per protocol. Eleven months after the end of treatment the child is in complete tumor remission. In children with hepatic tumor and ITE, combination of normothermic extracorporeal circulation with cardioplegia and in situ hypothermic liver preservation allows "en bloc" extended hepatectomy and removal of ITE, with limited risk of postoperative liver failure.

The aim of surgery for hepatoblastoma (HB) is complete resection of the tumor without rupture. If the tumor has an intra-atrial tumor extension (ITE), combination of hepatobiliary and cardiac surgical techniques is needed. In case of extended hepatectomy leaving a small liver remnant, normothermic vascular exclusion exposes the patient to the risk of postoperative acute liver failure, which may lead to urgent liver transplantation (LT). To reduce this risk and allow complex liver resections, three techniques of hypothermic liver preservation (HLP) have been described: in situ, ante situm and ex situ HLP.

The aim of this article is to report on our experience of "en bloc" resection of a large HB of the right liver with ITE in a 3-year-old child combining in situ HLP and cardioplegia under normothermic extracorporeal circulation (ECC).

1. Case report

1.1. Case presentation

A 32-month-old male was presented with abdominal pain and vomiting. Physical examination revealed a large abdominal mass. Imaging with Ultrasound-Doppler (US) and computed tomography

Abbreviations: AA, Ascending Aorta; CT, computed tomography; ECC, extracorporeal circulation; HB, hepatoblastoma; HLP, hypothermic liver preservation; ITE, intra-atrial tumor extension; IVC, Inferior Vena Cava; LT, liver transplantation; SIOPEL, International Childhood Liver Tumors Strategy Group of the SIOP: Société Internationale d'Oncologie Pédiatrique; SVC, Superior Vena Cava; US, ultrasound.

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(CT) showed a large hepatic tumor of the right liver located in segments V, VI, VII and I measuring 9.4 × 9.0 × 12.8 cm, and a small satellite lesion of 1.2 cm diameter in segment V (Fig. 1). The main tumor extended into the right hepatic vein, the Inferior Vena Cava (IVC) and the right atrium, where its size was 3.5 × 3 cm. Its left edge touched the median hepatic vein. Portal branches were free of tumor. There was no intraperitoneal rupture and no distant metastasis. Alphafetoprotein level was 384 000 μg/L. Percutaneous ultrasound guided needle core biopsy confirmed the diagnosis of HB. Neither portal, nor central venous emboli were observed. The radiological staging was PRETEXT II V3 according to the International Childhood Liver Tumors Strategy Group (SIOPEL) staging [1]. The patient was treated according to the SIOPEL IV high risk protocol, using cisplatin and doxorubicin [2]. Due to good tumor response and poor tolerance to chemotherapy, the third preoperative cycle was skipped.

1.2. Situation at surgery and description of intervention

Eleven weeks after diagnosis CT showed a significant reduction of the main tumor with an estimated volumetric reduction of 90% (Fig. 1). Nevertheless, tumor persisted in the right atrium with tight contact and possible invasion of its posterior wall. Alphafetoprotein markedly decreased (168 μg/L at day of surgery). The remaining liver free of tumor included segments II, III, left $^2/_3$ of IV and left half of I, with left vessels. Its mass was estimated by CT volumetry between 200 and 250 g, representing 1.5–1.8% of the child's body mass.

The operation took place 13 weeks after diagnosis at the age of 35 months (weight 13.35 kg) and can be watched in Video 1. It was carried out through a median sternotomy, prolonged by an inversed T laparotomy. In situ HLP was prepared as follows (Fig. 2): 1) the inferior mesenteric vein was cannulated up to the splenomesenteric confluence; 2) the lower IVC was cannulated up to the renal veins; 3) the right branch of the portal vein was cut and a cannula was inserted in its proximal segment toward the left portal vein; 4) the infrahepatic IVC and the suprahepatic IVC were isolated. The hepatectomy started without vascular exclusion of the liver at the right border of the common trunk of the median and left hepatic veins, preserving the left $^2/_3$ of segment IV, and progressed toward the origin of the right portal pedicle. The lower retrohepatic IVC was freed from the right liver, which remained attached only by the right hepatic vein and the ITE (Fig. 3). The superior vena cava (SVC)

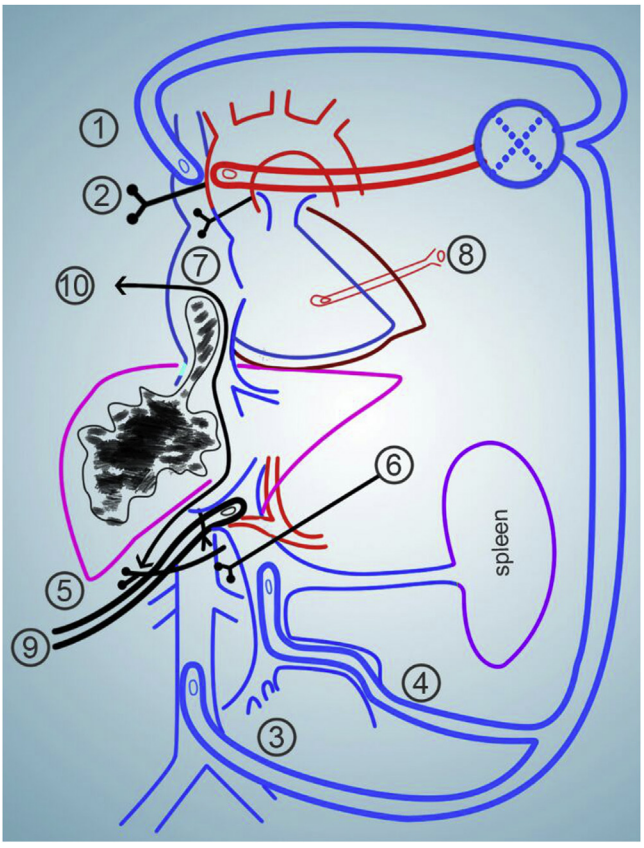

Fig. 2. Operation scheme. 1. SVC cannula, 2. SVC clamp, 3. IVC cannula, 4. Portomesenteric cannula, 5. Infra-hepatic suprarenal IVC clamp, 6. Hepatic pedicle clamp (Pringle's maneuver), 7. Right atrium opening for heart and liver remnant drainage, 8. Left atrium drainage cannula, 9. Portal cannula (through right portal stump) for in situ liver remnant perfusion of 4 °C preservation solution, 10. "En bloc" hepatectomy and ITE resection line.

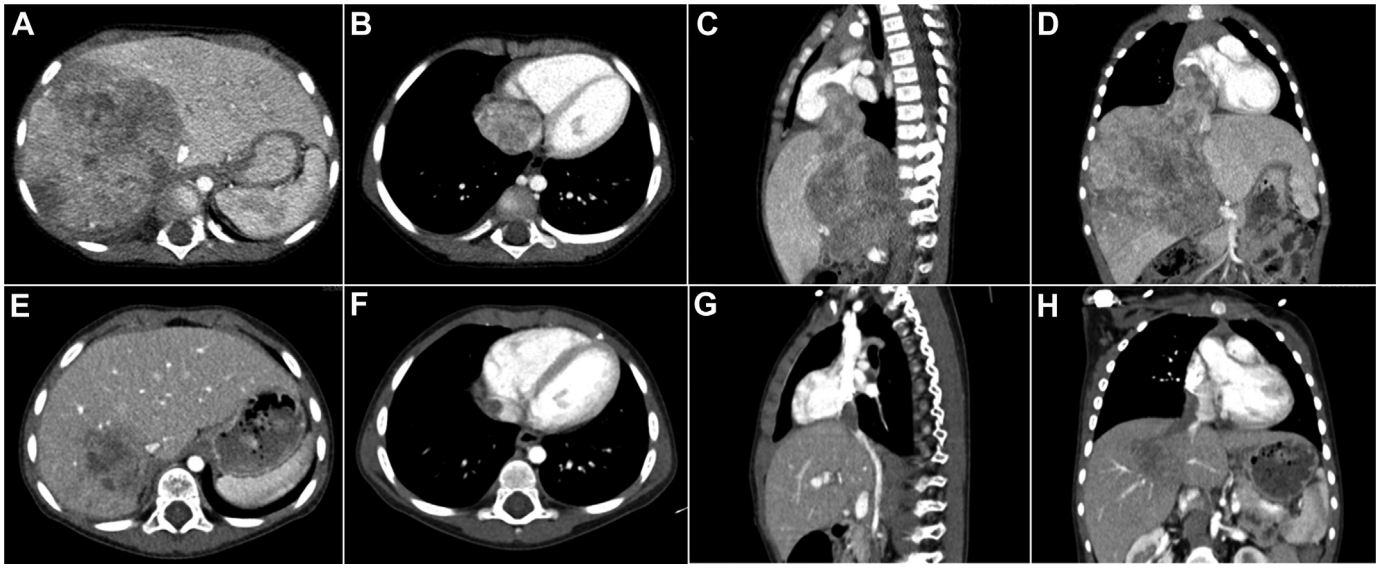

Fig. 1. Radiological presentation on injected CT of the tumor at diagnosis (A–D) and after 2 courses of chemotherapy (SIOPEL IV HR) at the time of surgery (E–H). Size at diagnosis was 94 × 90 × 128 mm for the main liver tumor and 36 × 28 mm for the tumor in the right atrium; pre-operatively the main tumor was reduced to 48 × 40 × 49 mm and the tumoral extension to the IVC and the right atrium to 11 × 11 × 27 mm.

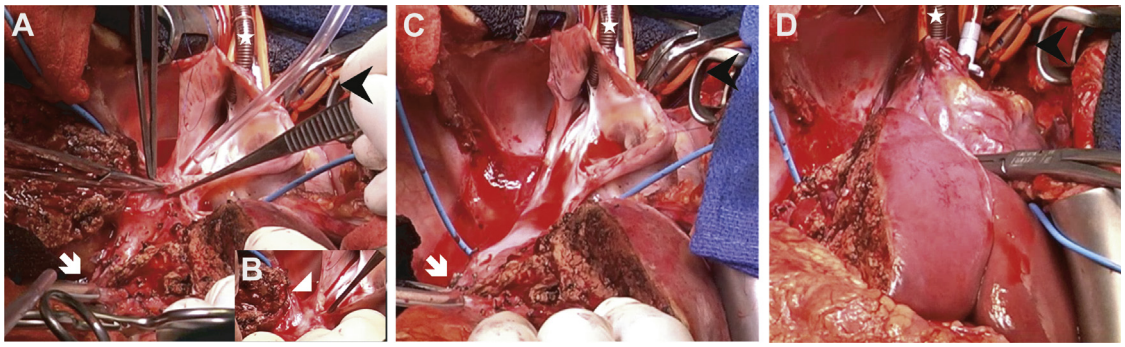

Fig. 3. Intraoperative views. A) The hepatectomy has been started without vascular exclusion, and the tumoral right liver remains attached only by the right hepatic vein and ITE. The heart was then arrested under cardioplegia and normothermic ECC: SVC cannula (star) and aortic cannula (black arrowhead). HLP was achieved by clamping the hepatic pedicle and infusion of 4 °C preservation solution through a cannula inserted in the right portal vein stump (white arrow). The atrium is opened for both cardiac and hepatic outflow drainage. B) Magnification of the intra-atrial tumor extension (white triangle) on a different view. C) The tumor has been resected "en bloc" with the ITE and the IVC and atrial vascular wall. D) The right atrium has been reconstructed with an autologous pericardial patch. The heart has been restarted, while the liver remains excluded with the newly reconstructed suprahepatic IVC clamped.

and the ascending aorta (AA) were cannulated to complete the installation for ECC. After insertion of a cannula in the AA for cardioplegia, the AA and the SVC were clamped, a cannula was inserted in the left atrium for drainage and cardioplegia was started. After cardiac arrest the diaphragm was opened longitudinally and total vascular exclusion of the liver was immediately carried out by: 1) clamping of the hepatic pedicle, 2) clamping of the suprarenal, infrahepatic IVC, 3) opening of the right atrium for drainage and 4) infusion of cold (4 °C) preservation solution (Custodiol®, *EUSA Pharma*, Germany) in the left liver via the right portal cannula. The drained fluid from the right atrium was not reused. As the ITE was tightly adherent to the posterior wall of the right atrium, it was resected "en bloc" with the IVC and ITE, and the hepatectomy was finalized (Fig. 3). There was no tumor rupture during the procedure and the margins were macroscopically free of tumor. An autologous pericardial patch was used to reconstruct the right atrium and the IVC (Fig. 3). The cold perfusion of the liver was stopped and the remaining left liver was flushed with 300 mL of cold (4 °C) 5% albumin. The newly reconstructed IVC was clamped below the diaphragm, and the heart was restarted, with the liver remnant still being under total vascular exclusion. The cardiac function was immediately good. The HLP perfusion cannula was removed of the right portal vein stump, and the liver remnant was reperfused by declamping the infrahepatic IVC, suprahepatic IVC and the hepatic pedicle. Reperfusion of the liver remnant was immediate and homogenous and the child was hemodynamically stable: the ECC was stopped and the remaining cannulas were removed. Heparin was antagonized with protamine. Two pericardial drains and a left thoracic drain were placed. Two pairs of electrodes were inserted on the right atrium and on the left ventricle for further stimulation, if needed. An immediate postoperative US showed normal vascular flows in the liver remnant.

Duration of ECC was 110 min, cardioplegia 53 min and liver remnant cold ischemia time was 66 min. Intraoperative blood products (including albumin) transfused represented 4.3 times patient's total blood volume. Additional fluids administrated during the procedure represented 1.4 times patient's total blood volume. No vasopressors were needed.

1.3. Postoperative course

The postoperative (po) course was almost uneventful, apart from one recurrent episode of clostridium difficile colitis, and the child was discharged home on po day 20. Histological examination of the resected specimen showed complete macro- and microscopic resection (R0). Forty percent of the tumor remnant was viable HB, whose histology was 95% fetal type, 4% embryonic and 1% of small undifferentiated cells. The ITE was sterilized by chemotherapy. One month after surgery chemotherapy was resumed as per SIOPEL IV high risk protocol [2]. Overall tolerance was good. Currently, 11 months after the end of treatment, and 14 months after surgery, the child is alive and well in complete tumor remission with normal liver function tests.

2. Discussion

2.1. Surgical challenges posed by hepatic tumors with ITE

HB is a malignant tumor whose cure needs surgery aiming at complete resection without tumor rupture [3–6]. As ITE of HB is rare, there is no consensus on surgical techniques to remove it. Goals of surgery must be "en bloc" resection of both tumoral liver and ITE without tumor rupture, and prevention of postoperative liver failure. In favorable cases, the ITE is not adherent to the vascular wall, and shrinks after pre-op chemotherapy: in such cases, the lower part of the right atrium can be clamped through the abdominal incision, and the intravascular tumor remnant can be extracted together with the main hepatic tumor after opening the IVC. In cases where the intra-atrial tumor remnant is large and/or adhesion or invasion of the atrial wall is suspected, opening the right atrium ± resection of the vascular wall seems to be the most cautious option to avoid tumor rupture and spillage, and allow complete (R0) resection: in such cases cardioplegia is needed.

2.2. Techniques used for hepatic tumors with ITE

In adults, Hepatocellular Carcinoma (HCC) can present with intravascular extension to the IVC and the right atrium [7]. Tumors with extension in the IVC can be safely resected with good long term results using varying degrees of vascular exclusion [8–10]. "En bloc" resection provides a clear survival benefit for adults with HCC [11,12]. In cases of ITE current recommendation is to start with hepatectomy and proceed as far as possible before cardiac surgery, in order to reduce the time of cardioplegia [11]. Since the upper IVC needs to be opened for such "en bloc" resection, the perfusion of the liver remnant needs to be interrupted temporarily, leading to the risk of ischemia-reperfusion injury. To reduce the risk of normothermic ischemic injury, a standard approach was cardioplegia combined with general hypothermia [13,14]. The general hypothermia can be as deep as 18 °C and combined with a

Table 1
Reported cases of hepatoblastoma with intra-atrial extension.

Study	Age, gender	Liver extension	Intraportal and/or extrahepatic tumor apart from ITE	Pre-op chemo	Type of resection	En bloc	Cold liver preservation	Follow up
Patients who underwent hepatectomy with atrial resection or thrombectomy								
Mestres et al., 1991 [32]	36, M	VI to VIII	No	3 cycles	Right hepatectomy with atrial resection	Yes	General hypothermia (20 °C) with circulatory arrest	Death po day 21 (probably pulmonary embolism)
Murakami et al., 1995 [33]	36, M	Local recurrence after right hepatectomy	No	Yes	Complementary resection with atrial resection	No	Cardiopulmonary bypass without liver preservation	Death 12 M post op, intracranial bleeding due to metastasis
Oldhafer et al., 2000 [16]	31, ?	I + IV to VIII	IVC, right renal vein, portal vein	3 cycles	Extended right hepatectomy with atrial resection	Presumably no: caval thrombectomy separately from the main tumor	General hypothermia (20 °C) with low-flow perfusion	Local recurrence; A&W, free of tumor, 10 months after second line treatment[a]
Wang et al., 2002 [34]	27, M	Right lobe	Lung Portal vein	yes	Not specified	?	?	Alive 24 M post op; no details available
Wang et al., 2002 [34]	17, M	Right + left multifocal	Lung portal vein	yes	Not specified	?	?	Death 28 M post op
Freely et al., 2010 [35]	11, F	I to IV	No	2 cycles	Left hepatectomy with atrial resection	Yes	Hypothermia (32 °C) with cardiopulmonary bypass	No follow up data available
Guérin et al., 2010 [36]	?	All	Lung	7 cycles	Liver transplant vascular thrombectomy without atrial resection[b]	Yes R1 resection[b]	Primary LT ECC without cardioplegia[b]	Lung recurrence; A & W, free of tumor, 8 years after second line treatment[b]
Lautz et al., 2011 [37]	8, F	PRETEXT IV P2V3 (central), POST-TEXT III P1V3 (central)	No	Yes	Non anatomical resection + atrial thrombectomy	Not specified R1 resection	Cardiopulmonary bypass without liver preservation	Liver ischemia Rescue LT (living donor); A&W, free of tumor, 11 M after LT
Other cases of intra-atrial HB mentioned in literature								
Sarper et al., 2006 [38]	10, ?	All segments multifocal	Portal vein	8 cycles	No resection	–	–	Alive 43 M post diagnosis with residual disease
Pepelassis et al., 2007 [39]	25, M	?	No	Yes	?	?	?	No follow-up data available; Shrinkage of ITE + reopening of IVC under chemotherapy
Kesik et al., 2009 [40]	18, M	Bifocal: right lobe + IV B PRETEXT IV	No	6 cycles	Only right hepatectomy as thrombus resolved	–	No	A&W, free of tumor 11 M after diagnosis
Huang et al., 2010 [41]	48, M	V to VIII (± IV ?)	Lung	2 cycles	–	–	–	Death by fungal meningitis related to Chemotherapy

? : unspecified
[a] Local tumor recurrence 6 and 11 months after initial surgery, above the right kidney and below the right diaphragm, treated by 2 further surgical resections, high dose chemotherapy with autologous stem cell transplantation, and local radiotherapy.
[b] Personal communication with Dr. Florent Guérin: recurrent pulmonary metastasis resected 5 months after LT.

low-flow perfusion [15]. This technique was implemented by Oldhafer et al., in children [16]. Although general hypothermia is commonly used in children for surgery of congenital heart defects, it increases the risk of bleeding due to coagulopathy [17]. In case of hepatectomy with liver cut surface, bleeding may be a life threatening risk after unclamping the liver remnant. To circumvent both risks of normothermic liver ischemia and bleeding due to general hypothermia, in situ HLP has been described in adults [18,19].

2.3. Techniques to reduce the risk of postoperative liver failure

Postoperative liver failure may be due to: 1) insufficient mass of the liver remnant, 2) preexisting dysfunction of the liver parenchyma (for instance in cirrhotic patients), 3) ischemia-reperfusion injury during the surgical procedure. The "small for size syndrome" is a well-known complication after LT, when the graft/patient weight ratio is below 1% [20,21]. After in situ HLP, the liver remnant is in a similar situation to a liver graft after LT. In our patient the estimated liver remnant/patient weight ratio was 1.5-1-.8%, which was considered to be adequate after in situ HLP, but dangerous after prolonged normothermic liver exclusion. Standard warm ischemia is normally achieved by hepatic pedicle clamping (Pringle's maneuver), which significantly reduces intraoperative hemorrhage [22]. However, in our patient cardiac surgery could have exceeded the standard maximum of 60 min, and thus putting the cardiac surgeon under pressure. For prolonged liver ischemia, Azoulay et al., showed better tolerance to ischemia by using in situ HLP compared to normothermic vascular exclusion [23].

2.4. Techniques for hypothermic liver preservation

Selective hypothermic perfusion of the liver has been described early in the history of liver surgery [24]. There are three main techniques of isolated (as opposed to systemic) hypothermic preservation of the liver: ex situ, ante situm and in situ techniques [25]. Pichlmayer described the method of ex vivo liver surgery, including total hepatectomy, ex situ preservation of the liver (as for a liver graft), complex partial hepatectomy, and re-implantation of the autograft [26]. This technique allows a maximal comfort for liver surgery (3D mobilization of the liver, no bleeding and reduced time pressure), but may have severe complications due to vascular and biliary reconstructions, especially the risk of hepatic artery thrombosis of the liver remnant [27,28]. Moreover, this technique is inappropriate, if the whole tumor cannot be removed by total hepatectomy alone: in case of ITE, the total hepatectomy would lead to transection of the tumor, which for HB would be equivalent to tumor rupture. In order to minimize complications of the ex situ technique, the "ante situm" approach was proposed, in which the hepatic pedicle is not transected and the liver is perfused with hypothermic solution in situ via the portal or arterial branch of the lobe that is resected in direction of the remaining liver, and drainage via the suprahepatic IVC, which is transected allowing high organ mobility [29]. However, this technique requires clamping of the suprahepatic IVC, and therefore cannot be used in case of atrial tumor extension. The third option is in situ hypothermic perfusion, in which there is no vascular transection, but only clamping of the supra- and infra-hepatic IVC. The liver is perfused as described in the ante situm technique and drained via an incision of the retrohepatic IVC. This technique can be combined with cardioplegia and atrial opening, which obviates the need of suprahepatic IVC clamping and allows "en bloc" resection of the hepatic tumor and its ITE. Based on their own experience and review of the literature Hoti et al., and Azoulay et al., favor in situ and ante situm techniques, rather than ex situ surgery: in a review of their experience and published cases, 23/205 (11.2%) patients died after in situ and ante situm HLP and none was transplanted; after ex situ HLP 17/62 (27.4%) patients died, and 8 needed salvage LTs of whom 7 eventually died [30,31].

2.5. Review of literature for hepatoblastoma with ITE

The prognosis of HB with intra-atrial extension is dismal in our review of 12 published cases over the last 25 years, as shown in Table 1 [16,32–41]. Three patients did not undergo surgery: one died, two were alive with tumor at last follow-up and presumably died. Nine patients underwent surgery, four died and five (42% of the 12 reported cases) are alive in complete remission with a follow-up ranging from 10 months to 8 years: one after rescue LT for liver ischemia, two after local or metastatic recurrence requiring second line treatment, one after right hepatectomy alone (as ITE resolved under chemotherapy), and one with limited details available. These results compare poorly with currents results of High Risk HBs: in the SIOPEL-4 trial [2] high risk patients had a 83% overall 3-year survival, and complete remission could be achieved in 46/62 patients (74%). This discrepancy between our reviews of published cases of HBs with ITE may be related to the continuous progress in the overall management of HB patients in the last decades, especially the improvement of risk-adapted chemotherapy regimens [2]. Noteworthy, however, in our review of the published HBs with ITE, complete resection without tumor rupture was reported in only 3/12 patients, including 1 whose ITE had resolved under chemotherapy.

3. Conclusion

In situ HLP combined with cardioplegia and normothermic ECC is a safe technique for surgery of hepatic tumors with ITE in children, enabling complete "en bloc" resection of the tumoral liver and the ITE, and reducing the risk of postoperative liver failure. It diminishes time pressure on both cardiac and hepatic surgical teams, and avoids the risks of general hypothermia.

Conflict of interest statement

None declared.

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Appendix. Supplementary data

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